Long-Term Care Updates

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Tofersen: a review of the first treatment targeting a genetic cause of ALS

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Indications:

Tofersen is FDA-approved for the treatment of amyotrophic lateral sclerosis (ALS) in patients with a superoxide dismutase 1 (SOD1) gene mutation.[1]

Tofersen was approved under accelerated approval; continued approval will depend on confirmatory trials demonstrating clinical benefit.[1]

Pharmacology:

Around 15% of patients with familial ALS have pathologic genetic variants in SOD1, which cause misfolding and accumulation of toxic proteins.[2] Tofersen is an antisense oligonucleotide which binds to SOD1 mRNA, resulting in degradation of SOD1 mRNA and a reduction in SOD1 protein synthesis.[1]

Pharmacokinetics:

Tofersen is administered intrathecally, which allows for distribution from the cerebral spinal fluid (CSF) to central nervous system (CNS) tissues. Maximum trough concentrations in the CSF are observed after the 3rd dose (last dose of loading period), and little to no accumulation in the CSF occurs with monthly dosing after the loading period. Tofersen moves from the CSF to systemic circulation, with a time to maximum plasma concentration (T_{max}) of 2-6 hours. No accumulation of tofersen in plasma is reported with monthly maintenance dosing. Age, body weight, race, and sex do not appear to alter exposure to tofersen, while the impact of hepatic or renal impairment on tofersen's pharmacokinetic profile has not been studied. [1] Additional pharmacokinetic parameters of tofersen are listed in Table 1.

Table 1: Available pharmacokinetic parameters for tofersen.[1]

	Tofersen
Absorption	T_{max} (plasma) = 2-6 hours
Distribution	Distributed throughout CNS tissues
Metabolism	Exonuclease (3' and 5')-mediated hydrolysis
Excretion	Primary route of excretion has not been characterized. $t_{1/2\ (CSF)}$ = 4 weeks

Standard of Care/Clinical Guidelines:

The American Academy of Neurology (AAN) last updated its practice parameter addressing drug, nutritional, and respiratory therapies for patients with ALS in 2009 (reaffirmed 2023).[3] With respect to drug therapy, the AAN concluded that riluzole is safe and modestly effective for slowing disease progression, leading to a recommendation that riluzole should be offered to patients with ALS (Level A: Established as Effective). Due to insufficient evidence, the AAN does not offer a recommendation for or against the use of lithium carbonate in patients with ALS. The AAN does not support the use of creatine (Level A: Established as Ineffective) or high-dose vitamin E (Level B: Probably Ineffective) in patients with ALS.[3]

While the AAN practice parameter was reaffirmed by the Academy in 2023, it has not been updated to include edaravone (approved for ALS in 2017) or sodium phenylbutyrate/taurursodiol (approved for ALS in 2022). Experts recommend both edaravone and sodium phenylbutyrate / taurursodiol in patients with ALS who are taking or unable/unwilling to take riluzole (weak recommendation; moderate-quality evidence).[2]

Due to its approval date, tofersen's place in therapy is not addressed by the AAN practice parameter. However, experts recommend its use in patients with ALS due to pathologic variants in SOD1 (weak recommendation; low-quality evidence).[2]

Clinical Efficacy:

Tofersen was granted accelerated FDA-approval on the basis of one phase III trial which enrolled 108 patients with weakness attributed to ALS and confirmed SOD1 gene mutation . Of the study population, 42 unique SOD1 gene mutations were identified. The primary analysis was conducted in patients meeting the criteria for "faster-progressing disease." The primary endpoint was the change in ALS Functional Rating Scale-Revised (ALSFRS-R) total score. This tool consists of 12 items across four subdomains, including bulbar function, fine motor function, gross motor function, and breathing function. Total ALSFRS-R scores can range from 0 to 48, and higher scores indicate better function. Key secondary endpoints included changes in SOD1 concentrations in the CSF, changes in neurofilament light chain concentrations in the plasma, time to death or permanent ventilation, and time to death. Tofersen did not significantly improve ALSFRS-R total scores when compared with placebo. Additionally, no difference in the time to death or permanent ventilation was reported between groups. However, tofersen therapy was associated with significant reductions in SOD1 concentrations in the CSF and neurofilament light chain concentrations in the plasma when compared with placebo. SOD1 concentrations were decreased by 29% with tofersen and increased by 16% with placebo. Similarly, neurofilament light chain concentrations were decreased by 60% with tofersen and increased by 20% with placebo.[4]

A long-term evaluation of tofersen's safety, pharmacokinetics, pharmacodynamics, and clinical effects in patients with ALS and confirmed SOD1 mutation is ongoing, with study completion estimated mid-2024.[5]

Adverse Reactions:

The most common adverse reactions reported with tofersen include pain, fatigue, arthralgia, CSF white blood cell increases, myalgia, CSF protein increases, musculoskeletal stiffness, and neuralgia (Table 2). Less common adverse reactions include myelitis and/or radiculitis; papilledema and elevated intracranial pressure; and aseptic meningitis. Long-term use has been associated with pyrexia.

Table 2: Commonly reported adverse reactions to tofersen.[1]

	Tofersen (n = 72)	Placebo (n = 36)
Arthralgia	14%	6%
CSF Protein Increase	8%	3%
CSF White Blood Cell Increase	14%	0%
Fatigue	17%	6%
Musculoskeletal Stiffness	6%	0%
Myalgia	14%	6%
Neuralgia	6%	0%
Pain	42%	22%

Boxed Warning:

Tofersen does not carry a Boxed Warning.[1]

QT Prolongation:

Tofersen is not associated with prolongation of the QTc interval when given at the maximum approved dosing regimen.[1]

Contraindications, Warnings & Precautions:

Tofersen carries no labeled contraindications. In clinical research, serious cases of myelitis and/or radiculitis; papilledema and elevated intracranial pressure; and aseptic meningitis have been reported. While all cases of papilledema, elevated intracranial pressure, and aseptic meningitis were appropriately managed without the need to discontinue tofersen, some patients experiencing myelitis and/or radiculitis required discontinuation of tofersen therapy. Patients should be monitored for signs and symptoms associated with these adverse reactions, with appropriate diagnostic workup and treatment initiated according to standard of care. Interruption or discontinuation of tofersen therapy may be required in patients experiencing myelitis and/or radiculitis.[1]

Drug Interactions:

Clinically significant drug interactions with tofersen are unlikely. In vitro studies show that tofersen is not a substrate, inhibitor, or inducer of CYP450 enzymes or major transporters. However, clinical drug interaction studies have not been conducted.[1]

Recommended Monitoring:

Laboratory monitoring is not required with tofersen. However, patients should be monitored for signs and symptoms associated with myelitis, radiculitis, papilledema, elevated intracranial pressure, and aseptic meningitis.[1]

Geriatric/Nursing Considerations:

In the phase III clinical trial for tofersen, 13.5% and 1.2% of patients were aged ≥65 years and ≥75 years, respectively. No differences in safety or effectiveness were observed between younger versus older patients. However, greater sensitivity to tofersen in older patients cannot be ruled out.[1]

Dosing and Availability:

Tofersen is available as a 100mg/15mL single-dose vial for intrathecal injection.[1]

Usual Adult Dosage**:**

- Loading period: 100mg every 14 days for a total of 3 doses
- Maintenance period: 100mg every 28 days

Renal Dosing: Tofersen has not been studied in patients with renal impairment.

Hepatic Dosing: Tofersen has not been studied in patients with hepatic impairment.

Geriatric Dosing: Refer to adult dosing.

Summary:

1. Tofersen is an antisense oligonucleotide approved for the treatment of ALS in patients with SOD1 gene mutations.
2. Clinical practice guidelines have not addressed tofersen's place in therapy; however, its role is likely limited to patients with ALS due to pathologic variants in SOD1, representing around 15% of patients with familial ALS.
3. In a 28-week, phase III clinical trial, tofersen did not improve scores associated with ALS severity and progression or reduce the risk of death or permanent ventilation; however, significant decreases in SOD1 concentrations and neurofilament light chain concentrations were reported with tofersen over placebo. Tofersen's continued approval is contingent on confirmatory trials demonstrating clinical benefit.
4. The most common adverse reactions reported with tofersen include pain, fatigue, arthralgia, CSF white blood cell increases, myalgia, CSF protein increases, musculoskeletal stiffness, and neuralgia. Less commonly, myelitis, radiculitis, papilledema, elevated intracranial pressure, and aseptic meningitis have been reported with tofersen.
5. Tofersen does not prolong the QTc interval, has limited potential to cause drug-drug interactions, and does not require close laboratory monitoring.
6. Tofersen is administered intrathecally via lumbar puncture at a dose of 100mg, with a loading phase consisting of 3 doses given at 14-day intervals apart and a maintenance phase consisting of 5 doses given at 28-day intervals.

References:

1. Qalsody [package insert]. Cambridge, MA: Biogen MA Inc.; April 2023.
2. Goyal NA, Galvez-Jiminez N, Cudkowicz ME. Disease-modifying treatment of amyotrophic lateral sclerosis. In: UpToDate. Available at: https://www.uptodate.com/contents/disease-modifying-treatment-of-amyotrophic-lateral-sclerosis. Updated May 9, 2023. Accessed October 6, 2023.
3. Miller RG, Jackson CE, Kasarskis EJ, et al. Practice parameter update: the care of the patient with amyotrophic lateral sclerosis: drug, nutritional, and respiratory therapies (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology.* 2009;73(15):1218-1226.
4. Miller TM, Cudkowicz ME, Genge A, et al. Trial of antisense oligonucleotide tofersen for SOD1 ALS. *N Engl J Med*. 2022;387(12):1099-1110.
5. Long-Term Evaluation of BIIB067 (Tofersen). Available at: https://clinicaltrials.gov/study/NCT03070119. Updated May 22, 2023. Accessed October 6, 2023.